Organic Acid Metabolism Disorders

Propionic Acidemia (PA)

Propionic acidemia (PA) is a disorder of isoleucine (ILE), methionine (MET), threonine (THR), valine (VAL), and odd chain fatty acid metabolism caused by deficient activity of the enzyme propionyl coenzyme A carboxylase. This enzyme deficiency leads to the accumulation of toxic organic acid metabolites when the affected infant is ingesting a normal diet or is under catabolic stress.

Inheritance:	Autosomal recessive
Estimated Incidence:	1:100,000
Abnormal Screen Result:	Elevated C3 (propionyl carnitine) Elevated C3/C2
Method of Notification:	All results where the C3 is greater than 10 μM and the C3/C2 is elevated are called to physician of record. All results where the C3 is greater than 15 μM are called to the physician of record regardless of the C3/C2. Any other abnormal C3 results are mailed to the physician of record.
Next Steps if Abnormal:	**Potential medical emergency when the C3 is greater than 10 μM and the C3/C2 is elevated or when the C3 is greater than 15 μM regardless of the C3/C2.** See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Repeat acyl carnitine profile as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist.
Neonatal Presentation:	Poor feeding, vomiting, tachypnea, lethargy, abnormal muscle tone, involuntary movements, seizures, coma
Treatment:	Protein restricted diet. Use of metabolic formula without ILE, MET, THR, VAL. Carnitine supplementation. Biotin trial.

USpecial Considerations

Fasting/infection/intercurrent illness—Parents must clearly understand that minor illnesses can precipitate metabolic decompensation in an infant/child with an organic acid disorder and should seek medical attention with any concern. Urinary ketones may be monitored as a precaution during illness. Ketonuria can be an early sign of metabolic decompensation and frequently precedes clinical signs.

Methylmalonic Acidemia (MMA)

Methylmalonic academia (MMA) is a disorder of isoleucine (ILE), methionine (MET), threonine (THR), valine (VAL), and odd chain fatty acid metabolism caused by deficient methylmalonyl CoA mutase, deficient Vitamin B12 (cobalamin) or defects in absorption, transport or processing of cobalamin. Toxic organic acid metabolites accumulate when the affected infant is ingesting a normal diet or is under catabolic stress.

Inheritance:	Autosomal recessive
Estimated Incidence:	Vit B 12 non-responsive 1:48,000 Other types, unknown incidence
Abnormal Screen Result:	Elevated C3 (propionyl carnitine) Elevated C3/C2 Elevated C3/C16
Method of Notification:	All results where the C3 is greater than 10 μM and the C3/C2 is elevated are called to physician of record. All results where the C3 is greater than 15 μM are called to the physician of record regardless of the C3/C2. Any other abnormal C3 results are mailed to the physician of record.
Next Steps if Abnormal:	**Potential medical emergency when the C3 is greater than 10 μM and the C3/C2 is elevated or when the C3 is greater than 15 μM regardless of the C3/C2.** See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Repeat acyl carnitine profile as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist.
Neonatal Presentation:	Poor feeding, vomiting, tachypnea, lethargy, abnormal muscle tone, involuntary movements, seizures, coma
Treatment:	Trial of hydroxycobalamin as soon as suspected. Protein restricted diet. Use of metabolic formula without ILE, MET, THR, VAL. Carnitine supplementation.

Special Considerations

Fasting/infection/intercurrent illness—Parents must clearly understand that minor illnesses can precipitate metabolic decompensation in an infant/child with an organic acid disorder and should seek medical attention with any concern. Urinary ketones may be monitored as a precaution during illness. Ketonuria can be an early sign of metabolic decompensation and frequently precedes clinical signs.

Malonic Acidemia (MA)

Malonic academia (MA) is a disorder of ketone metabolism caused by deficient malonyl CoA decarboxylase. Although it is not a disorder of branched chain amino acid metabolism, it is typically included with other organic acid disorders because the subsequent organic aciduria includes methylmalonic acid derived from the catabolism of isoleucine (ILE) and valine (VAL) in addition to the malonic aciduria.

Inheritance:	Autosomal recessive
Estimated Incidence:	Unknown, thought to be very rare
Abnormal Screen Result:	Elevated C3DC (malonyl carnitine)
Method of Notification:	All abnormal results called to physician of record
Next Steps if Abnormal:	See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Repeat acyl carnitine profile as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist.
Neonatal Presentation:	May have hypotonia, hypoglycemia, hypertrophic cardiomyopathy, diarrhea, vomiting, ketosis and/or seizures
Treatment:	Carnitine supplementation. May be prescribed fat controlled diet with medium chain triglyceride (MCT) oil as major fat source.

Special Considerations

Fasting/infection/intercurrent illness—Parents must clearly understand that minor illnesses can precipitate metabolic decompensation in an infant/child with this disorder and should seek medical attention with any concern.

Isobutyryl coA Dehydrogenase Deficiency (IBCD)

Isobutyryl coA dehydrogenase deficiency (IBCD) is a disorder of valine metabolism. Infants with this disorder may have cardiomyopathy and anemia.

Inheritance:	Presumed autosomal recessive
Estimated Incidence:	Unknown, thought to be very rare
Abnormal Screen Result:	Elevated C4 (butyryl carnitine)
Method of Notification:	All abnormal results called to physician of record
Next Steps if Abnormal:	See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Repeat acyl carnitine profile as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist.
Neonatal Presentation:	None
Treatment:	Carnitine supplementation. Moderate protein restriction and avoidance of fasting may be helpful.

Isovaleric Acidemia (IVA)

Isovaleric acidemia (IVA) is a disorder of leucine (LEU) metabolism caused by deficiency of the enzyme isovaleryl coA dehydrogenase. This enzyme deficiency leads to the accumulation of toxic organic acid metabolites when the affected infant is ingesting a normal diet or is under catabolic stress. NOTE: A chronic, intermittent form of IVA can present later in infancy of childhood with episodes of metabolic acidosis, usually associated with an intercurrent illness or increased protein intake.

Inheritance:	Autosomal recessive
Estimated Incidence:	1:230,000
Abnormal Screen Result:	Elevated C5 (isovaleryl carnitine)
Method of Notification:	All abnormal results called to physician of record
Next Steps if Abnormal:	**Potential medical emergency.** See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Repeat acyl carnitine profile as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist.
Neonatal Presentation:	Poor feeding, vomiting, tachypnea, lethargy, abnormal muscle tone, involuntary movements, seizures, coma
Treatment:	Protein restricted diet. Use of metabolic formula without LEU. Glycine (GLY) supplementation. Carnitine supplementation.

Special Considerations

Fasting/infection/intercurrent illness—Parents must clearly understand that minor illnesses can precipitate metabolic decompensation in an infant/child with an organic acid disorder and should seek medical attention with any concern. Urinary ketones may be monitored as a precaution during illness. Ketonuria can be an early sign of metabolic decompensation and frequently precedes clinical signs.

2-Methylbutyryl coA Dehydrogenase Deficiency (2-MBCD)

2-Methylbutyryl coA dehydrogenase deficiency (2-MBCD) is a disorder of isoleucine (ILE) metabolism. Infants with this disorder may be asymptomatic or may have an episode of metabolic decompensation with subsequent neurological deficits.

Inheritance:	Presumed autosomal recessive
Estimated Incidence:	Unknown, thought to be very rare outside of persons of Hmong ancestry
Abnormal Screen Result:	Elevated C5 (isovaleryl carnitine)
Method of Notification:	All abnormal results called to physician of record
Next Steps if Abnormal:	See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Repeat acyl carnitine profile as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist.
Neonatal Presentation:	Hypotonia, lethargy, apnea, hypoglycemia
Treatment:	Carnitine supplementation. Moderate protein restriction. Avoid fasting.

3-Methylcrotonyl coA Carboxylase Deficiency (3-MCC)

3-Methylcrotonyl coA carboxylase deficiency (3-MCC) is a disorder of leucine (LEU) metabolism. Infants may have a Reye-like illness with hypoketotic hypoglycemia, hypotonia, hepatic encephalopathy, and metabolic acidosis. Symptomatic infants may have a "cat's urine" odor.

Inheritance:	Autosomal recessive
Estimated Incidence:	1:50,000
Abnormal Screen Result:	Elevated C5OH (3-OH isovaleryl carnitine)
Method of Notification:	All abnormal results called to physician of record
Next Steps if Abnormal:	See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Repeat acyl carnitine profile as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist.
Neonatal Presentation:	Usually none. May present with seizures.
Treatment:	Carnitine supplementation. Moderate protein and LEU restriction. Glycine supplementation. Avoid fasting. NOTE: Biotin is not effective in isolated 3-MCC.

Special Considerations:

Maternal 3-MCC—In some newborns, the elevated C5OH is reflective of maternal 3-MCC.

Beta Ketothiolase Deficiency

Beta ketothiolase deficiency (SKAT) is a disorder of isoleucine (ILE) metabolism and of ketolysis. Infants with this disorder are at risk for episodes of severe ketoacidosis with subsequent neurological deficits. This disorder is sometimes called 2-methyl 3-OH butyric aciduria.

Inheritance:	Autosomal recessive
Estimated Incidence:	Unknown
Abnormal Screen Result:	Elevated C5OH (3-OH isovaleryl carnitine) Elevated C5:1 (tiglyl carnitine)
Method of Notification:	All abnormal results called to physician of record
Next Steps if Abnormal:	See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Repeat acyl carnitine profile as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist.
Neonatal Presentation:	Poor feeding, vomiting, tachypnea, lethargy
Treatment:	Carnitine supplementation. Protein restricted/fat controlled diet. Avoid fasting. May require long term bicarbonate.

Special Considerations

Fasting/infection/intercurrent illness—Parents must clearly understand that minor illnesses can precipitate metabolic decompensation in an infant/child with an organic acid disorder and should seek medical attention with any concern. Urinary ketones should be monitored at home. Ketonuria can be an early sign of metabolic decompensation and frequently precedes clinical signs.

3 **Methyl 3-OH Glutaryl co-A Lyase Deficiency (HMGL)**

3 methyl 3-OH glutaryl co-A lyase (HMGL) deficiency is a disorder of leucine (LEU) metabolism and of ketogenesis. Infants with this disorder may present with hypoketotic hypoglycemia and are at risk for subsequent neurological deficits.

Inheritance:	Autosomal recessive
Estimated Incidence:	Unknown, thought to be rare
Abnormal Screen Result:	Elevated C5OH (3-OH isovaleryl carnitine) Elevated C6DC (3-methyl glutaryl carnitine)
Method of Notification:	All abnormal results called to physician of record
Next Steps if Abnormal:	See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Repeat acyl carnitine profile as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist.
Neonatal Presentation:	One-third of affected newborns will have hypoketotic hypoglycemia, severe metabolic acidosis, vomiting, lethargy, hypotonia
Treatment:	Protein restricted diet. Use of metabolic formula without LEU. Carnitine supplementation. Fat controlled diet when older. Avoid fasting.

Special Considerations

Fasting/illness/protein loading—Parents must clearly understand that minor illness can precipitate metabolic decompensation in an infant/child with this disorder and should seek medical attention with any concern. Protein loading or fasting can also lead to hypoglycemic episodes result in seizures or coma.

3 Methylglutaconyl co-A Hydratase Deficiency

3 Methylglutaconyl co-A hydratase deficiency is a disorder of leucine (LEU) metabolism. It is sometimes known as 3 methylglutaconic aciduria type I. Three other types of 3 methylglutaconic aciduria have also been described. Mildly affected persons have speech retardation and short attention span. Severely affected persons have had acidosis and more severe neurological problems, hypotonia, spastic dystonia, irritability, developmental delay and mental retardation.

Inheritance:	Autosomal recessive
Estimated Incidence:	Unknown, thought to be very rare
Abnormal Screen Result:	Elevated C5OH (3-OH isovaleryl carnitine)
Method of Notification:	All abnormal results called to physician of record
Next Steps if Abnormal:	See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Repeat acyl carnitine profile as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist
Neonatal Presentation:	None reported
Treatment:	Carnitine supplementation. Moderate protein and LEU restriction. Avoid fasting.

Multiple Carboxylase Deficiency (MCD) or Holocarboxylase Synthetase Deficiency

Multiple carboxylase deficiency (MCD) is caused by a deficiency of the enzyme holocarboxylase synthetase. This enzyme activates four carboxylases by attaching biotin. These carboxylases are involved in amino acid metabolism, gluconeogenesis, and fatty acid synthesis. Affected infants may develop severe metabolic acidosis leading to coma. Skin rash and hair loss occur at later stages.

Inheritance:	Autosomal recessive
Estimated Incidence:	1:87,000
Abnormal Screen Result:	Elevated C3 (propionyl carnitine) Elevated C5OH (3-OH isovaleryl carnitine)
Method of Notification:	All results where both C3 and C5OH are elevated are called to the physician of record.
Next Steps if Abnormal:	See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Repeat acyl carnitine profile as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist
Neonatal Presentation:	May show food refusal, vomiting, lethargy, seizures, hypotonia, tachypnea
Treatment:	Biotin supplementation

Special Considerations

Enzymes necessary for carboxylase activity—Two enzymes are necessary for normal activity of four carboxylases: holocarboxylase synthetase to attach biotin to the carboxylases and biotinidase to free the protein bound biotin.

Glutaric Aciduria Type I (GA I)

Glutaric aciduria type I (GA I) is caused by a deficiency in the enzyme glutaryl coA dehydrogenase. Seventy percent of infants will have macrocephaly at or shortly after birth. Infants may remain asymptomatic until an encephalopathic crisis. Others gradually develop motor delay and hypotonia without any apparent acute crisis. No loss of intellectual capacity develops unless a neurological crisis occurs.

Inheritance:	Autosomal recessive
Estimated Incidence:	1:40,000
Abnormal Screen Result:	Elevated C5DC (glutaryl carnitine)
Method of Notification:	All abnormal results called to physician of record
Next Steps if Abnormal:	**Potential medical emergency.** See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Repeat acyl carnitine profile as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist.
Neonatal Presentation:	Macrocephaly, irritability, jitteriness, hypotonia
Treatment:	Prompt treatment of catabolic events. Aggressive fever control. Watch fluid intake, as affected persons may have profuse sweating. Riboflavin trial. Carnitine supplementation. Protein restricted diet. Use of metabolic formula without lysine (LYS) and tryptophan (TRP).

Special Considerations

Fasting/infection/intercurrent illness—Parents must clearly understand that minor illnesses can precipitate encephalopathic or metabolic decompensation in an infant/child with this disorder. Hospital admission may be considered mandatory for IV fluids with any vomiting illness.

Fever—Poorly controlled/untreated persons with GA I may have recurrent fever not related to illness. Death from hyperthermia has been reported in children with GA I.

Acute subdural and/or retinal hemorrhages—Infants with GA I are prone to acute subdural and/or retinal hemorrhage after minor head trauma (ie, minor childhood falls that can occur when infant is learning to walk) that can be misdiagnosed as child abuse.

2-Methyl 3-OH Butyric Aciduria

2-methyl 3-OH butyric aciduria (2M3HBA) is a disorder of isoleucine (ILE) metabolism and of 2-methyl branched chain fatty acids. Infants with this disorder are at risk for episodes of metabolic decompensation, usually after a stressor. Reported cases have shown progressive loss of motor skills, choreoathetosis, dystonia and seizures.

Inheritance:	Thought to be X-linked, but an affected female has been identified.
Estimated Incidence:	Unknown, thought to be very rare
Abnormal Screen Result:	Elevated C5OH (3-OH isovaleryl carnitine) Elevated C5:1 (tiglyl carnitine)
Method of Notification:	All abnormal results called to physician of record
Next Steps if Abnormal:	See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Repeat acyl carnitine profile as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist.
Neonatal Presentation:	Usually none
Treatment:	ILE and protein restricted diet